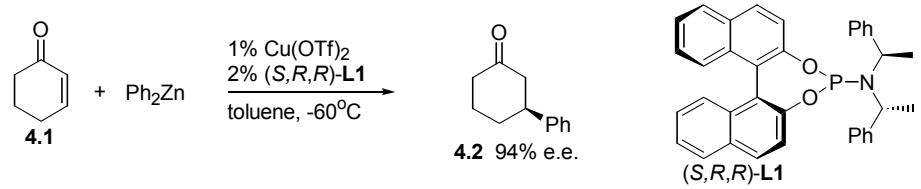
Asymmetric catalysis with chiral monodentate phosphoramidite ligands

Duursma, Ate

Chapter 4
Asymmetric conjugate addition of phenylboronic acid to nitroalkenes

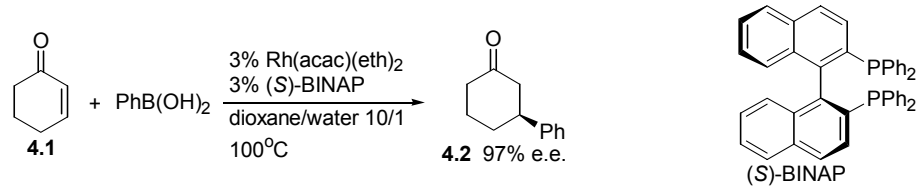
4.1 Introduction

The asymmetric conjugate addition (ACA) of dialkylzinc reagents, catalyzed by a copper-phosphoramidite complex, is an effective tool for the enantioselective construction of C-C bonds, as shown in the preceding chapters. It has a broad scope with respect to substrates and di*alkyl*zinc reagents that can be used. In contrast, the ACA of di*aryl*zinc reagents, has received far less attention.[1-3] However, Diego Peña in our group recently demonstrated that excellent enantioselectivity can be obtained in the ACA of diphenylzinc with a copper-phosphoramidite catalyst based on **L1** (Scheme 4.1).[4]



Scheme 4.1 *Copper-catalyzed ACA of diphenylzinc.*

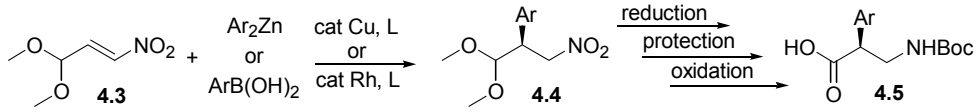
A more established method for the enantioselective introduction of aryl groups is the rhodium-BINAP catalyzed ACA of arylboronic acids introduced in 1998 by Miyaura and Hayashi (Scheme 4.2).[5;6]



Scheme 4.2 *Rhodium-catalyzed ACA of phenylboronic acid.*

In Chapter 3 the catalytic enantioselective synthesis of a β^2-amino acid and its derivatives is described, based on the ACA of a dialkylzinc reagent to nitroalkene **4.3**. Our goal was to increase the scope of this route by the synthesis of β^2-amino acids with aromatic substituents. Therefore both the copper-catalyzed ACA of diarylzinc as well as the

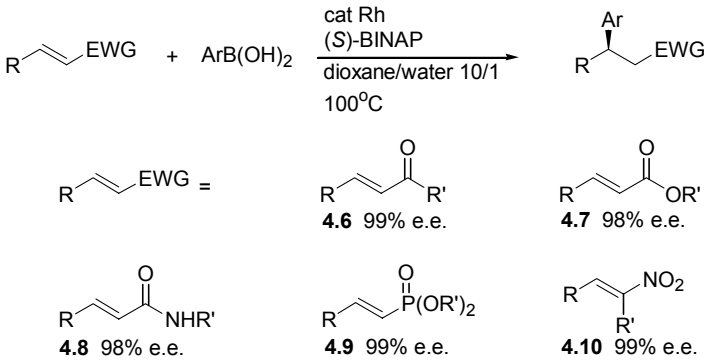
rhodium-catalyzed ACA of arylboronic acid was investigated as a way to synthesize β^2-amino acid compounds **4.5** with aromatic substituents (Scheme 4.3).



Scheme 4.3 *Proposed route to β^2-amino acids with aromatic substituents.*

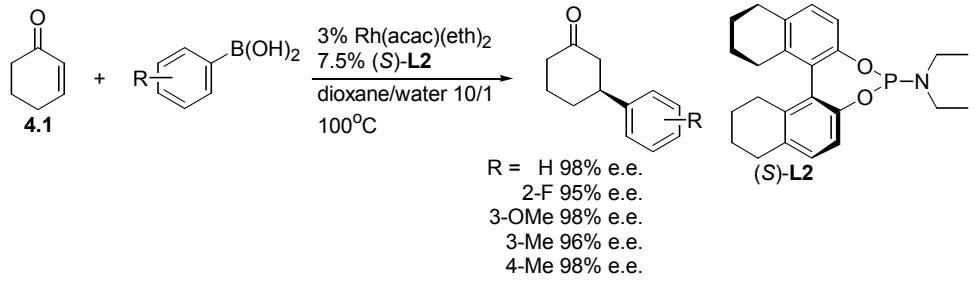
4.2 Earlier work

The rhodium-BINAP catalyzed ACA of aryl- and alkenylboronic acids is a highly convenient method for the formation of an sp^2-sp^3 C-C bond and the simultaneous introduction of a new stereogenic center.[7] Due to its high enantioselectivity for a wide range of substrates and arylboronic acids it is currently the most frequently applied method for the enantioselective conjugate addition of aryl groups. An overview of the different classes of substrates that have been successfully employed, including the e.e. values for the corresponding arylated products, is given in Scheme 4.4. A more detailed overview can be found in two recent reviews.[7,8]



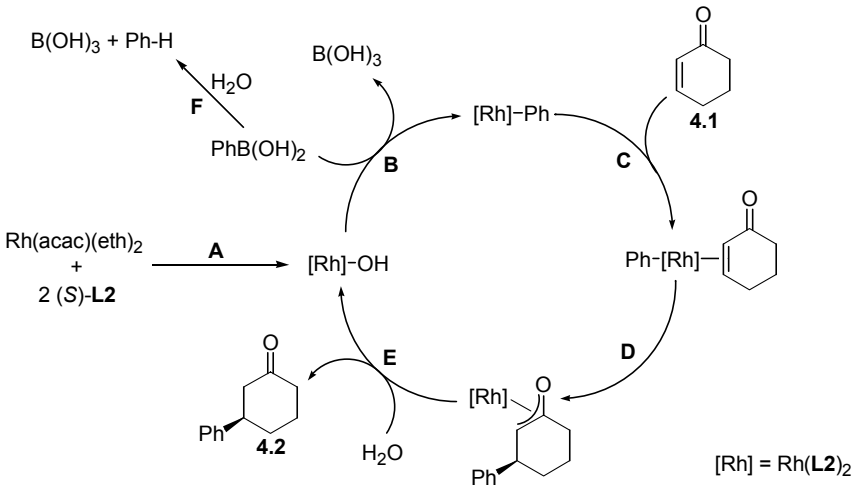
Scheme 4.4 *Overview of linear substrates used in the rhodium-catalyzed ACA of arylboronic acids.*

In contrast to the wide variety of substrates and organoboron compounds that are used, BINAP is almost exclusively employed as the chiral ligand. Although modified versions of this ligand can give rise to higher e.e. values,[9,10] they are rarely used due to their difficult synthesis. The facile and modular synthesis of the monodentate phosphoramidites prompted our group to investigate their application as chiral ligands for the rhodium-catalyzed ACA of arylboronic acids. Roos Imbos and Jean-Guy Boiteau have found that phosphoramidites are extremely effective ligands for the rhodium-catalyzed ACA of arylboronic acids to cyclic enones.[11-13] The e.e. values are similar to those obtained with BINAP, while the reaction rate is greatly enhanced. The use of phosphoramidite **L2** leads to >95% e.e. in the ACA of various arylboronic acids to cyclohexenone (Scheme 4.5).



Scheme 4.5 *Rhodium-phosphoramidite catalyzed ACA of arylboronic acids.*

These results are even more impressive when the relatively harsh reaction conditions are taken into account. Phosphoramidite ligands rapidly hydrolyze in acidic media, but it was found that the rhodium-phosphoramidite complex is very stable in these media.[11] The need for water and the relatively high reaction temperature can be explained by the mechanism of the rhodium-catalyzed ACA (Scheme 4.6), which has been thoroughly investigated for the rhodium-BINAP catalyst by Hayashi.[14]



Scheme 4.6 *Proposed catalytic cycle for the rhodium-phosphoramidite catalyzed ACA.*

The high temperature is needed to displace the acetylacetonate (acac) and to generate the catalytically active hydroxorhodium species (**A**). A subsequent transmetalation of the phenyl group from boron to rhodium leads to the formation of a phenylrhodium complex and $B(OH)_3$ (**B**). Coordination of the substrate (**C**) is followed by the enantioselective insertion of **4.1** into the phenyl-rhodium bond, giving an oxa-π-allyl species (**D**). Hydrolysis of this species gives the desired phenylated product **4.2** and regenerates the catalytically active hydroxorhodium species (**E**). Water acts as a proton donor and facilitates the transmetalation, and is therefore essential in order to complete the catalytic cycle. A drawback of the use of water, especially in combination with the high temperature,

is hydrolysis of phenylboronic acid to benzene (**F**). The arylboronic acid is therefore added in excess (3-5 eq.) compared to the enone.

Two other types of chiral ligands that have been successfully applied in rhodium-catalyzed ACA of phenylboronic acid to cyclohexenone are diphosphonite **4.11** by Reetz,[15] and amidophosphine **4.12** by Tomioka (Figure 4.1).[16,17]

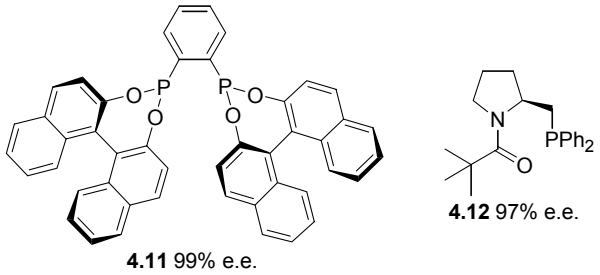
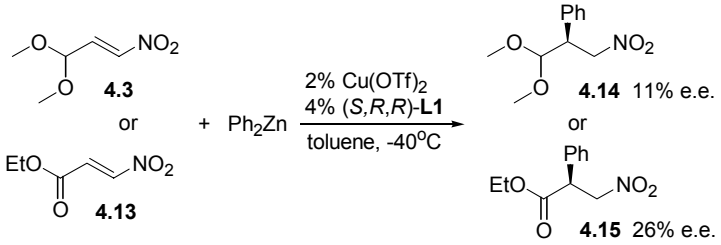


Figure 4.1 *Other ligands used for the ACA of arylboronic acids.*

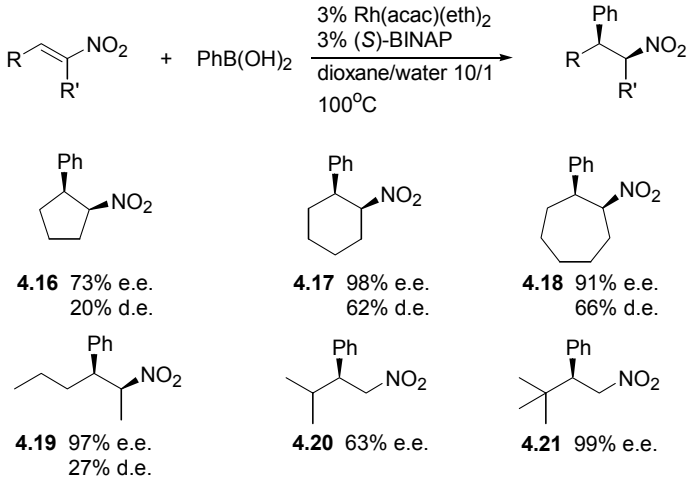
4.3 Conjugate additions to aliphatic nitroalkenes

Combining the results obtained in the copper-catalyzed ACA of dialkylzinc reagents to nitroalkenes (Chapter 3) and those shown in Scheme 4.1, led to the use of nitropropene acetal **4.3** and nitroacrylate **4.13** as substrates for the ACA of diphenylzinc (Scheme 4.7).



Scheme 4.7 *ACA of diphenylzinc to aliphatic nitroalkenes.*

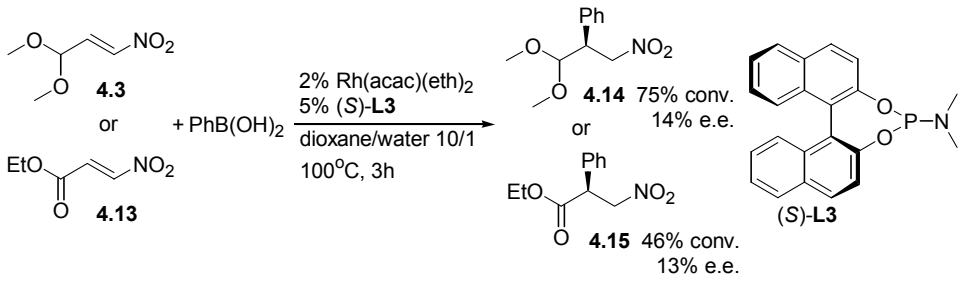
Although the nitroalkenes are completely converted to the corresponding phenylated products, the reactions are rather slow (17 h), the e.e. values are low (11-26%), and biphenyl is formed as a byproduct. The absence of an uncatalyzed reaction leaves little room for improvement by changing the conditions, although a different ligand might be able to do so. In addition to this, the limited availability of diarylzinc reagents can be seen as a drawback. Therefore we decided to explore the rhodium-catalyzed ACA of phenylboronic acid as a way to obtain these products. Hayashi has also used nitroalkenes as substrates, which led to excellent e.e. values for the corresponding products in several cases (Scheme 4.8).[18]



Scheme 4.8 *Rhodium-BINAP catalyzed ACA of phenylboronic acid to nitroalkenes.*

High enantioselectivities are found when α-substituted nitroalkenes are used as substrates, although the diastereoselectivity is much lower (**4.16-4.19**). The formation of diastereomers can be avoided with the use of nitroalkenes which lack α-substituents, but the enantioselectivity (63% for **4.20**) or the yield (5% for **4.21**) is much lower is those cases.

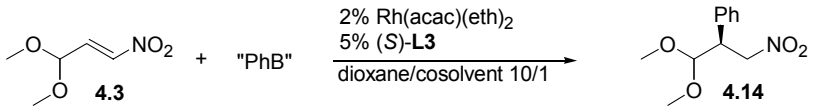
Similar observations were made in our case as the ACA of phenylboronic acid to nitroalkenes **4.3** and **4.13** resulted in moderate conversions and low e.e. values with a rhodium-phosphoramidite catalyst based on **L3** (MonoPhos) (Scheme 4.9).



Scheme 4.9 *Rhodium-phosphoramidite catalyzed ACA of phenylboronic acid to nitroalkenes.*

The moderate conversion might be explained by hydrolysis of the acetal or ester moiety, or by decomposition of the catalyst during the reaction. In order to prevent this, different conditions were screened (Table 4.1).

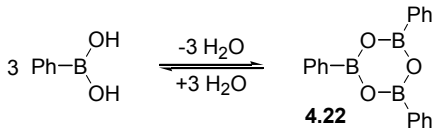
Table 4.1 *Conditions for the ACA of phenylboronic acid to **4.3**.*



entry	"PhB"	temp.	cosolv.	additive	time (min)	conv. (%)[a]	e.e. (%)[a]
1	$PhB(OH)_2$	100°C	H_2O	-	180	75	14
2	$PhB(OH)_2$	100°C	MeOH	-	30	100	14
3	$PhB(OH)_2$	50°C	MeOH	-	180	0	-[b]
4	$PhB(OH)_2$	50°C	MeOH	Et_3N	180	100	1
5	$PhB(OH)_2$	50°C	MeOH	DBU	30	100	-[b]
6	$(PhBO)_3$	100°C	H_2O	-	180	59	10
7	$(PhBO)_3$	100°C	MeOH	-	30	100	14

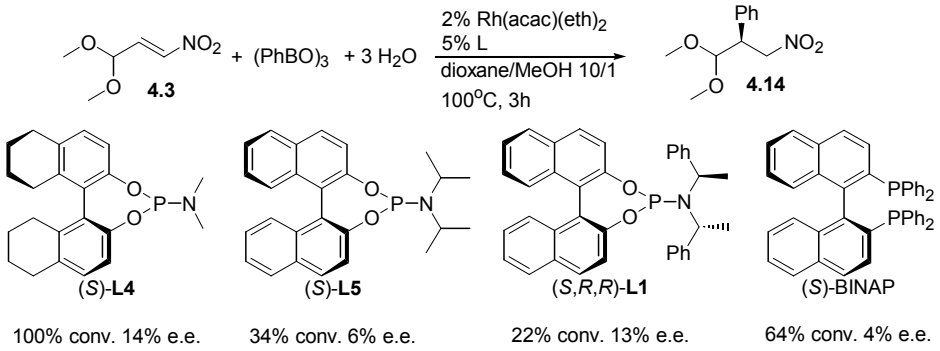
[a]Determined by chiral GC, [b]no product observed.

Replacing water (entry 1) by methanol (entry 2) as a proton source had a beneficial effect upon the reaction. Complete conversion was obtained within 30 min, although the enantioselectivity did not improve. The e.e. might be increased by lowering the reaction temperature to 50°C, but this probably prevents the dissociation of the acetylacetonate as no conversion was observed (entry 3). From the work of Miyaura it is known that the addition of bases can facilitate this process at lower temperatures,[19] and therefore Et_3N and DBU were added to the reaction mixture at 50°C. Although the reaction does proceed to complete conversion, the addition of Et_3N has a detrimental effect upon the enantioselectivity (entry 4) whereas DBU is incompatible with **4.3** (entry 5). Phenylboronic acid is most often used as the organoboron reagent for the rhodium-catalyzed ACA, but exists in equilibrium with its trimeric species, phenylboroxine (**4.22**) (Scheme 4.10).[20]



Scheme 4.10 *Equilibrium between phenylboronic acid and phenylboroxine.*

Hayashi has demonstrated that in-situ formation of phenylboronic acid through the use of phenylboroxine and 1 equivalent of water with respect to boron, rather than the use of phenylboronic acid itself, can lead to higher e.e. values.[10] In our case the use of phenylboroxine gives almost identical results compared to phenylboronic acid (entries 6,7). Under these optimized conditions three other phosphoramidites were tested as chiral ligands for the ACA of phenylboroxine (Scheme 4.11).

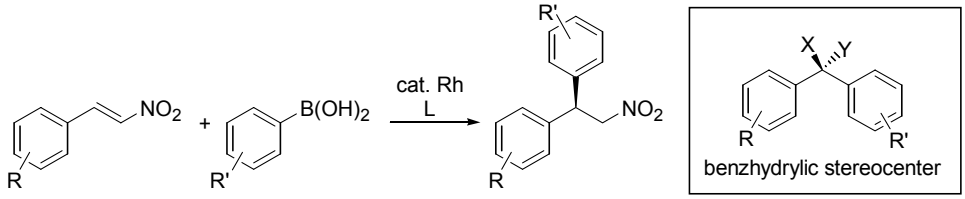


Scheme 4.11 *Ligand screening.*

Use of ligand **L4** leads to results comparable to **L3**, whereas ligands with more bulky amine substituents like **L5** and **L1** lead to lower conversions and e.e. values. As already mentioned by Hayashi, BINAP is not a suitable ligand (4% e.e.) for the ACA of phenylboronic acids to nitroalkenes which lack α-substituents. Although the use of phosphoramidites as chiral ligands leads to better results, the obtained e.e. values are not sufficient for applications like the enantioselective synthesis of β^2-amino acids. Therefore we decided to focus on the use of aromatic nitroalkenes as substrates.

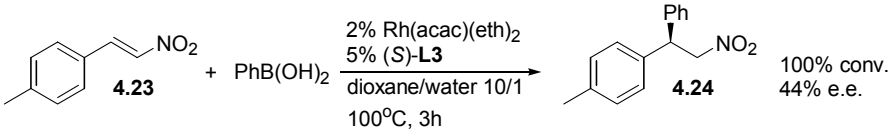
4.4 Conjugate additions to aromatic nitroalkenes

The ACA of an arylboronic acid to a nitrostyrene leads to the formation of a benzhydrylic stereogenic center, which is a frequent motif in natural products and pharmaceuticals (Scheme 4.12).[21,22]



Scheme 4.12 *Formation of a benzhydrylic stereocenter.*

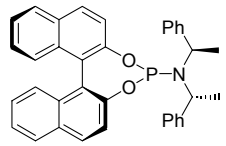
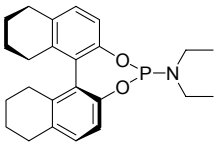
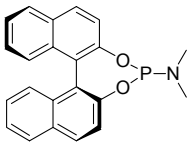
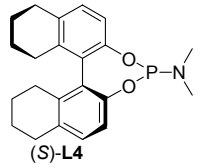
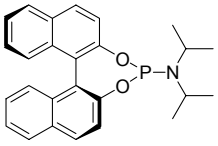
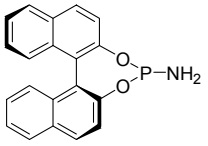
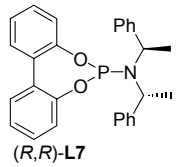
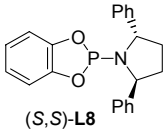
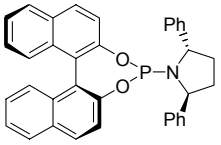
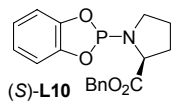
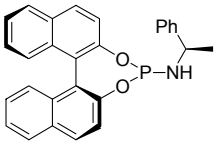
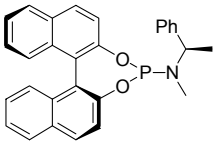
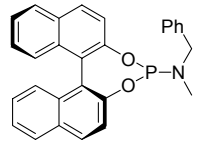
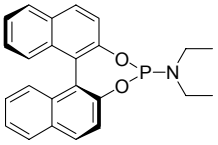
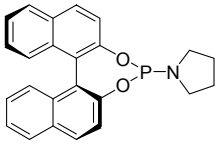
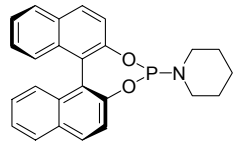
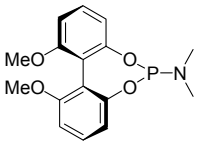
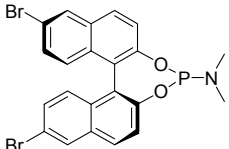
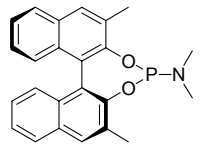
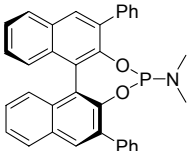
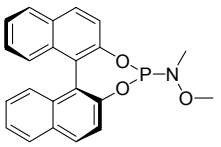
To our delight the reaction of phenylboronic acid with 4-methylnitrostyrene (**4.23**) resulted in complete conversion to the arylated product **4.24** with an e.e. of 44% (Scheme 4.13).



Scheme 4.13 *ACA of phenylboronic acid to **4.23**.*

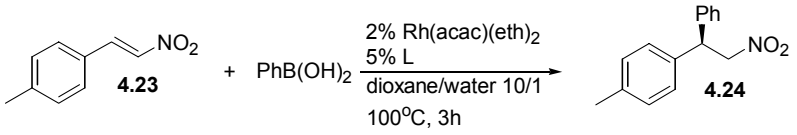
In contrast to nitroalkenes **4.3** and **4.13**, the standard reaction conditions (dioxane/water 10/1, 100°C) for the rhodium-catalyzed ACA are compatible with nitrostyrene **4.23**. Under these conditions a comprehensive set of phosphoramidite ligands was tested (Table 4.2)

Table 4.2 *Phosphoramidite ligands.*

 (*S*,*R*,*R*)-**L1**	 (*S*)-**L2**	 (*S*)-**L3**
 (*S*)-**L4**	 (*S*)-**L5**	 (*S*)-**L6**
 (*R*,*R*)-**L7**	 (*S*,*S*)-**L8**	 (*S*,*S*,*S*)-**L9**
 (*S*)-**L10**	 (*S*,*R*)-**L11**	 (*S*,*R*)-**L12**
 (*S*)-**L13**	 (*S*)-**L14**	 (*S*)-**L15**
 (*S*)-**L16**	 (*S*)-**L17**	 (*S*)-**L18**
 (*S*)-**L19**	 (*S*)-**L20**	 (*S*)-**L21**

For all reactions the conversion as well as the e.e. were measured every 30 min over a period of 3 h (Table 4.3).

Table 4.3 *Conversions and e.e. values.*



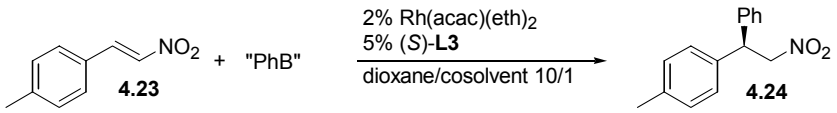
L	time	conv.[a]	e.e.[a]	L	time	conv.[a]	e.e.[a]
(*S*,*R*,*R*)-**L1**	180 min	0%	-	(*S*,*R*)-**L12**	180 min	83%	19%
(*S*)-**L2**	90 min	100%	44%	(*S*)-**L13**	30 min	100%	20%
(*S*)-**L3**	30 min	100%	44%	(*S*)-**L14**	30 min	100%	31%
(*S*)-**L4**	30 min	100%	48%	(*S*)-**L15**	30 min	100%	29%
(*S*)-**L5**	180 min	0%	-	(*S*)-**L16**	30 min	100%	40%
(*S*)-**L6**	180 min	0%	-	(*S*)-**L17**	30 min	100%	34%
(*R*,*R*)-**L7**	180 min	0%	-	(*S*)-**L18**	30 min	100%	45%
(*S*,*S*)-**L8**	30 min	100%	5%	(*S*)-**L19**	180 min	49%	9%
(*S*,*S*,*S*)-**L9**	180 min	22%	42%	(*S*)-**L20**	180 min	86%	0%
(*S*)-**L10**	180 min	54%	15%	(*S*)-**L21**	30 min	100%	38%
(*S*,*R*)-**L11**	180 min	69%	14%	(*S*)-BINAP	180 min	40%	11%

[a]Determined by chiral GC.

From these data it follows that phosphoramidite ligands with bulky substituents at the amine moiety give rise to inactive catalysts (**L1**, **L5**, **L7**). Ligand **L6** is probably not stable under these conditions, even in the form of a rhodium complex. Replacing the BINOL as the diol moiety by catechol (**L8**, **L10**) or biphenol (**L17**) leads to lower e.e. values. The introduction of substituents at the 3 and 3' positions of the BINOL lead to a sharp decrease in activity and selectivity (**L19**, **L20**). Phosphoramidite ligands based on BINOL and amines with unbranched alkyl substituents (**L2-4**, **L13-16**, **L18** and **L21**) display the highest activity and selectivity. Complete conversion is obtained within 30 min and the e.e. values are generally around 45%. Phosphoramidites can compete favorably with BINAP as chiral ligands for this reaction, due to their higher activity and selectivity. It proved to be unattainable so far to surpass the level of 48 % e.e. (**L4**) by variation of the amine moiety.

Consequently the conditions were modified, using the catalyst based on (*S*)-**L3**, in order to improve the enantioselectivity (Table 4.4).

Table 4.4 *Conditions for the ACA of phenylboronic acid to **4.23**.*



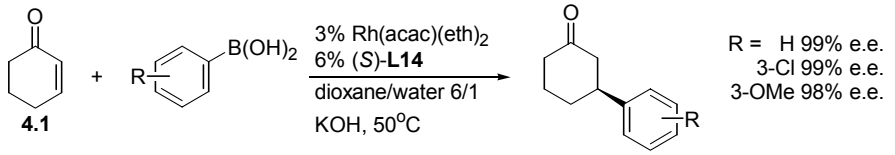
entry	"PhB"[a]	temp.	cosolv.	additive	time (min)	conv. (%)[b]	e.e. (%)[b]
1	$PhB(OH)_2$	100°C	H_2O	-	<5	100	44
2	$PhB(OH)_2$	100°C	MeOH	-	30	100	42
3	$PhB(OH)_2$	60°C	H_2O	-	30	100	44
4	$PhB(OH)_2$	50°C	H_2O	-	120	100	39
5	$PhB(OH)_2$	r.t.	H_2O	-	180	27	54
6	$PhB(OH)_2$	r.t.	H_2O	KOH	180	97	-[c]
7	$PhB(OH)_2$	r.t.	H_2O	Et_3N	420	95	50
8	$(PhBO)_3$	60°C	H_2O	-	30	100	35
9	$(PhBO)_3$	60°C	-	H_2O	90	100	46
10	$PhB(OH)_2$	100°C	H_2O	-	<5	100	32[d]
11	$PhB(OH)_2$	50°C	H_2O	-	120	100	37[d]

[a]4 equivalents, [b]determined by chiral GC, [c]no product observed, [d]new batch of $Rh(acac)(eth)_2$.

At 100°C the reaction is very fast, giving complete conversion within 5 min (entry 1). Water can be replaced by methanol without any problems, although neither a higher reaction rate nor e.e. are observed (entry 2). The e.e. can be raised by lowering the temperature, at the expense of the reaction rate (entries 3-5). As in the case of aliphatic nitroalkene **4.3** (Table 4.1), some bases are incompatible with the substrate (entry 6), whereas others increase the rate of the reaction (entry 7). The use of phenylboroxine as the organoboron compound leads to a lower e.e. when water is used as a cosolvent (entry 8), but gives slightly better results when only 1 equivalent of H_2O per boron is added (entry 9). The e.e. obtained at 50°C is somewhat lower than would be expected (entry 4), and when some of the experiments were repeated the obtained e.e. values were found to be lower. After a careful analysis of all the reagents and solvents it turned out that the rhodium precursor was responsible for this effect. A new batch of $Rh(acac)(eth)_2$ unfortunately led to even lower e.e. values for this reaction (entries 10,11), whereas it gave reproducible results for the reactions shown in scheme 4.5. Although phosphoramidites are good ligands for the rhodium-catalyzed ACA of arylboronic acids to nitroalkenes, the combination of moderate e.e. values and lack of reproducibility limit the practical application of this reaction.

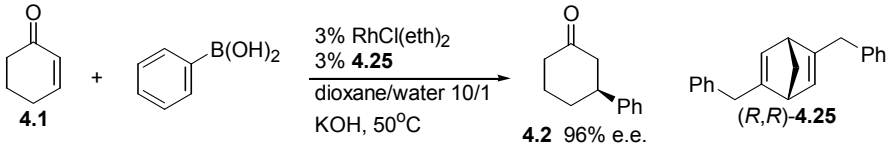
4.5 Further developments

Shortly after the publication of the results from our group,[12,13] the group of Miyaura demonstrated that phosphoramidite ligand **L14** is also an efficient ligand for the rhodium-catalyzed ACA of arylboronic acids to cyclic enones (Scheme 4.14).[23]



Scheme 4.14 *Rhodium-phosphoramidite catalyzed ACA of arylboronic acids.*

In a completely different, but very elegant, approach the group of Hayashi employed chiral diene **4.25** as a chiral ligand for the rhodium-catalyzed ACA of arylboronic acids to cyclic as well as acyclic enones (Scheme 4.15).[24]



Scheme 4.15 *A chiral chelating diene as a ligand.*

4.6 Conclusions

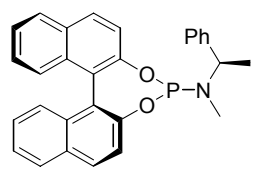
The ACA of aryl groups to nitroalkenes can be carried out in two different ways. The copper-phosphoramidite catalyzed ACA makes use of diphenylzinc as the organometallic reagent. In contrast to high enantioselectivities in the case of dialkylzinc reagents, the obtained e.e. values (up to 26%) for the arylated products of aliphatic nitroalkenes are rather low. This prevents an efficient enantioselective synthesis of β^2-amino compounds with aromatic substituents. The same holds for the other method, i.e. the rhodium-phosphoramidite catalyzed ACA of phenylboronic acid. Although the replacement of water by methanol led to complete conversion of the aliphatic nitroalkene to the arylated nitroalkane, the e.e. value remained low (14%) in a screening of different phosphoramidite ligands. Aromatic nitroalkenes are far better substrates for the rhodium-phosphoramidite catalyzed ACA of phenylboronic acid, and afford products with a benzhydrylic stereocenter. At 100°C 4-methyl-nitrostyrene (**4.23**) is completely converted to the desired product (**4.24**) within 5 min. The rhodium-phosphoramidite catalyst based on **L3** (MonoPhos) gives an e.e. value of 44% for **4.24**, which could be improved to 48% by the screening of 21 different phosphoramidite ligands. The most effective ligands are those with a small (achiral) amine moiety, which is in sharp contrast to bulky (chiral) amine moiety needed in the copper-catalyzed ACA (Chapter 3). The fast reaction allowed a further increase of the e.e. to 50% by lowering the temperature and the addition of a base,

which is a good result for a nitroalkene that lacks α-substituents. However, the obtained e.e. values of this reaction are highly dependent on the batch of the rhodium precursor, possibly due to impurities remaining from its synthesis. This makes the reaction irreproducible with respect to the enantioselectivity and limits the application of this reaction in the enantioselective synthesis of molecules with a benzhydrylic stereocenter.

4.7 Experimental section

General remarks.

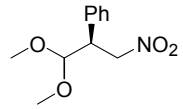
For general information see Chapter 2. Dioxane was distilled from sodium. Diphenylzinc and phenylboronic acid were purchased from Aldrich, stored at +6°C and used without purification. Nitroalkenes **4.3** and **4.13** were synthesized according to procedures described in Chapter 3. $Rh(acac)(eth)_2$ was purchased from Strem and immediately stored in a Schlenk vessel under a nitrogen atmosphere at +6°C. Phosphoramidite ligands (**L1**,[25] **L4**,[26] **L5**,[25] **L7**,[27] **L9**,[28] **L14**,[25] **L15**,[29] **L16**,[25] **L18**,[26] **L19**,[26] **L20**[25]) were synthesized according to literature procedures,[12,30] which are discussed in detail in Chapter 7. Several phosphoramidite ligands were kindly provided by Jean-Guy Boiteau (**L2**,[12] **L12**, **L17**,[13] **L21**[13]), DSM (**L3**[30]), Rob Hoen (**L8**,[31] **L10**[32]), Gerlof Kruidhof (**L6**[33]) and Diego Peña (**L11**,[34] **L13**[34]). Spectral data for ligands **L1-11** and **L13-21** can be found in the given references.

O,O'-(*S*)-(1,1'-dinaphthyl-2.2'-diyl)-N-methyl-N'-(*R*)-1-phenylethylphosphoramidite ((*S*,*R*)-L12). 

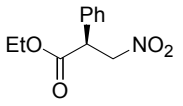
^{1}H-NMR δ: 8.03 (m, 4H), 7.57 (m, 13H), 4.88 (m, 1H), 2.06 (d, *J*= 10 Hz, 3H), 1.62 (d, *J*= 6.8 Hz, 3H); ^{13}C-NMR δ: 149.79 (d, *J*= 50 Hz), 141.70, 132.65 (d, *J*= 22 Hz), 130.95 (d, *J*= 60 Hz), 130.05 (d, *J*= 29 Hz), 128.25, 128.20 (d, *J*= 7 Hz), 127.62, 127.04 (d, *J*= 22 Hz), 127.01, 126.00 (d, *J*= 4 Hz), 124.60 (d, *J*= 20 Hz), 123.19 (d, *J*= 108 Hz), 121.91 (d, *J*= 19 Hz), 55.43 (d, *J*= 41 Hz), 26.74, 17.95 (d, *J* = 8 Hz); ^{31}P-NMR δ: 147.1. $[\alpha]_D$= +242° (c = 1.01, $CHCl_3$). HRMS calcd for $C_{29}H_{24}NO_2P$ 449.154 found 449.154.

General procedure A. Copper-phosphoramidite catalyzed ACA of diphenylzinc to nitroalkenes.

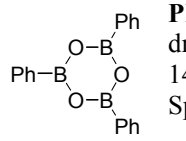
In a Schlenk tube 3.6 mg (0.01 mmol, 2 mol%) of $Cu(OTf)_2$ was flame-dried, and together with 10.8 mg (0.02 mmol, 4 mol%) of (*S*,*R*,*R*)-**L1** dissolved in 2 ml of dry toluene. After 30 min of stirring at room temperature 0.5 mmol of nitroalkene was added to the clear solution. The reaction mixture was cooled to -40 °C and 197 mg (0.9 mmol) of diphenylzinc was added. The reaction mixture was stirred at -40 °C until complete conversion (GC) and then poured into a mixture of 10 ml of saturated aqueous NH_4Cl and 10 ml of ethyl acetate. This mixture was rigorously stirred for 10 min. The aqueous layer was extracted twice with 40 ml of ethyl acetate and the combined organic layers were washed with brine and dried over Na_2SO_4, concentrated and purified with column chromatography.



(2,2-Dimethoxy-1-nitromethyl-ethyl)-benzene (4.14). According to general procedure **A**, 74 mg (0.5 mmol) of **4.3** gave 50 mg (0.2 mmol, 44% yield) of **4.14** as a colorless oil after column chromatography (pentane:diethyl ether 3:1 R_f 0.5). ^{1}H-NMR δ: 7.30 (m, 5H) 4.84 (dd, *J*= 13.0, 5.7 Hz, 1H), 4.68 (dd, *J*= 13.2, 9.2 Hz, 1H), 4.47 (d, *J*= 4.8 Hz, 1H), 3.81 (dt, *J*= 8.8, 5.4 Hz, 1H), 4.25 (m, 2H), 3.37 (s, 3H), 3.34 (s, 3H); ^{13}C-NMR δ: 135.9 (s), 128.7 (d), 128.4 (d), 127.8 (d), 106.3 (d), 76.0 (t), 56.0 (q), 55.0 (q), 47.4 (d). MS(CI) 243 ($M+NH_4^+$). Enantiomer separation on a CP Chiralsil CB column, 30m x 0.25 mm, 120°C isothermic, 86.4 / 88.5 min (GC). Or Chiralpak OB-H column, heptanes/isopropanol 97/3, 210nm, 25.6 / 28.7 min (HPLC).



3-Nitro-2-phenyl-propionic acid ethyl ester (4.15). According to general procedure **A**, 73 mg (0.5 mmol) of **4.13** gave 46 mg (0.2 mmol, 41% yield) of **4.15** as a colorless oil after column chromatography (pentane:diethyl ether 6:1 R_f 0.4). ^{1}H-NMR δ: 7.34 (m, 5H) 5.09 (dd, *J*= 14.4, 9.8 Hz, 1H), 4.51 (m, 2H), 4.18 (m, 2H), 1.22 (t, *J*= 7.2 Hz, 3H); ^{13}C-NMR δ: 170.5 (s), 133.3 (s), 129.3 (d), 128.6 (d), 127.8 (d), 75.7 (t), 61.8 (t), 48.7 (d), 13.9 (q). HRMS calcd for $C_{11}H_{13}NO_4$ 223.084 found 223.085. Enantiomer separation on a Chiraldex G-TA column, 30m x 0.25 mm, 120°C isothermic, 15.8 / 16.2 min (GC). Or Chiralpak AS column, heptanes/isopropanol 9/1, 210nm, 6.2 / 7.6 min (HPLC).

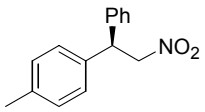


Phenylboroxine (4.22). According to a modified literature procedure.[10] In a drying pistol 3g (25 mmol) of phenylboronic acid was heated overnight at 145°C in vacuo to give 2.5g (8 mmol, 96% yield) of **4.22** as a white powder. Spectral data were in accordance with literature.[10]

General procedure B. Rhodium-phosphoramidite catalyzed ACA of phenylboronic acid to nitroalkenes.

In a Schlenk tube 2.58 mg (0.01 mmol, 2 mol%) of $Rh(acac)(eth)_2$ and 0.025 mmol (5 mol%) of phosphoramidite ligand were dissolved in 1 ml of anhydrous dioxane and stirred at room temperature for 15 min. 0.5 mmol of nitroalkene and 2.0 mmol of organoboron compound (4 equiv.) were added and the resulting mixture was stirred for 2 min. After the addition of 0.1 ml of water or methanol the mixture was degassed and stirred for 3 h at the indicated temperature. The reaction mixture was cooled to room temperature, quenched with saturated aqueous $NaHCO_3$ and extracted three times with diethyl ether. The combined organic layers were washed with brine and dried over Na_2SO_4, concentrated and purified with column chromatography.

When the course of the reaction (conversion and e.e.) was followed with chiral GC, 10 µl of n-tridecane was added as an internal standard and the initial sample was taken prior to the addition of the organoboron compound. During the reaction, aliquots of 0.1 ml were taken from the reaction mixture with a glass pipette and added to 1 ml of a stirred mixture of diethyl ether: saturated aqueous $NaHCO_3$ (1:1). After a few minutes the organic layer was decanted, filtered over Na_2SO_4, and subjected to GC or HPLC analysis.



2-Phenyl-2-(4-methylphenyl)-nitroethane (4.24). According to general procedure **B**, 82 mg (0.5 mmol) of **4.23** gave 72 mg (0.3 mmol, 60% yield) of **4.24** as a colorless oil after column chromatography (heptane:ethyl acetate 8:1 R_f 0.7). ^{1}H-NMR δ: 7.30 (m, 5H), 7.14 (s, 4H), 4.95 (m, 3H), 2.32 (s, 3H); ^{13}C-NMR δ: 139.9 (s), 137.2 (s), 136.1 (s), 129.6 (d) 128.9 (d), 127.5 (d), 127.4 (d), 79.2 (t), 48.5 (d), 20.9 (q). HRMS calcd for $C_{15}H_{15}NO_2$ 241.110 found 241.111. Enantiomer separation on a Chiralpak OJ column, heptanes/isopropanol 9/1, 210 nm, 14.1 / 18.3 min (HPLC).

4.8 References

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